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TITLE: Voxel-Wise Time-Series Analysis of Quantitative MRI in Relapsing-Remitting MS: Dynamic Imaging Metrics of Disease Activity Including Pre-Lesional Changes

PRINCIPAL INVESTIGATOR: Aaron S. Field, M.D., Ph.D.

CONTRACTING ORGANIZATION: University of Wisconsin  
Madison, Wisconsin 53715

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#### 14. ABSTRACT

Previous MRI studies in MS have retrospectively analyzed normal-appearing brain tissue in locations where typical MS lesions ultimately appeared, finding pre-lesional changes in several MRI metrics. However, studies have not been entirely consistent and the development of a prototypical MS lesion cannot as yet be prospectively predicted. The primary objective of this project is to validate the "preactive" lesion hypothesis in MS by identifying the spatiotemporal imaging signature of white matter destined to undergo acute, focal inflammation and demyelination—specifically, one that will allow reliable, prospective detection of nascent lesions before they appear on conventional (non-quantitative) imaging. The specific aim is to acquire a longitudinal set of quantitative MRI metrics in MS patients and perform a multivariate spatiotemporal analysis of pre-lesional, normal-appearing white matter, seeking spatially clustered interval changes that presage the appearance of a typical MS plaque.

Over the past year, the quantitative MRI protocol has been developed and optimized; enrollment and scanning of subjects is awaiting IRB approval of the study protocol, which is imminent.

#### 15. SUBJECT TERMS

Multiple sclerosis, magnetic resonance imaging, longitudinal studies, preactive lesions

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**INTRODUCTION:** Previous MRI studies in MS have retrospectively analyzed normal-appearing brain tissue in locations where typical MS lesions ultimately appeared, finding pre-lesional changes in several MRI metrics. However, studies have not been entirely consistent and the development of a prototypical MS lesion cannot as yet be prospectively predicted. The primary objective of this project is to validate the “preactive” lesion hypothesis in MS by identifying the spatiotemporal imaging signature of white matter destined to undergo acute, focal inflammation and demyelination—specifically, one that will allow reliable, prospective detection of nascent lesions before they appear on conventional (non-quantitative) imaging. The specific aim is to acquire a longitudinal set of quantitative MRI metrics in MS patients and perform a multivariate spatiotemporal analysis of pre-lesional, normal-appearing white matter, seeking spatially clustered interval changes that presage the appearance of a typical MS plaque.

**BODY:** We have completed the development and optimization of the quantitative MRI pulse sequences to be used for the project, summarized as follows: (1) myelin water mapping based on the mcDESPOT pulse sequence as originally reported by Deoni et al [1] and adapted by our group [2,3]; (2) magnetization transfer (MT) imaging as adapted and optimized by our group [4-9]; and hybrid diffusion imaging (HYDI), developed and optimized by our group [10-12]. Additionally, we developed the post-processing pipeline to be used for these multiparametric images, with key stages including brain extraction, co-registration of images from different modalities and time-points, and segmentation of normal-appearing white matter. We are currently enrolling and scanning subjects. Three subjects have been enrolled to date; one had to be dropped from the study because of an acute exacerbation in his disease that required him to begin disease-modifying therapy, which is one of the exclusion criteria.

**KEY RESEARCH ACCOMPLISHMENTS:** Novel approaches to improve the accuracy and reliability of quantitative MRI (qMRI) targeting cerebral white matter have been developed as detailed in previous progress reports. We are now scanning subjects and further accomplishments await completion of scanning in all subjects and data analysis.

**REPORTABLE OUTCOMES:** Several of our technical developments that preceded the initiation of scanning have been reported [2-9, 12]. Further reports now await completion of scanning in all subjects and data analysis.

**APPENDICES:** None.

**SUPPORTING DATA:**

The following abstracts resulting from this work were presented or accepted for presentation at national/international meetings since the previous reporting period:

1. Mossahebi P, Alexander AL, Field AS, Samsonov AA. Quantitative Magnetization Transfer Imaging With Non-Exchanging Compartment Modeling: From CSF Partial Volume Correction to More Accurate Characterization of White Matter. In: Proceedings of the International Society for Magnetic Resonance in Medicine (ISMRM) 21<sup>st</sup> Scientific Meeting, Salt Lake City, Utah, April 2013.
2. Mossahebi P, Alexander AL, Field AS, Samsonov AA. Analysis and Optimization of Quantitative Magnetization Transfer Imaging Considering The Effect of Non-Exchanging Component. Accepted for presentation at the International Society for Magnetic Resonance in Medicine (ISMRM) 22<sup>nd</sup> Scientific Meeting, Milan, Italy, May 2014.

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1. Deoni SC, Rutt BK, Arun T, Pierpaoli C, Jones DK. Gleaning multicomponent T1 and T2 information from steady-state imaging data. *Magn Reson Med* 2008;60:1372-1387.
2. Hurley SA, Mossahebi P, Samsonov AA, Alexander AL, Deoni SC, Fisher R, Duncan ID, Field AS. Multicomponent relaxometry (mcDESPOT) in the shaking pup model of dysmyelination. Proceedings of the International Society for Magnetic Resonance in Medicine (ISMRM) 18<sup>th</sup> Scientific Meeting, Stockholm, Sweden, May 1-7, 2010:88.
3. Hurley SA, Yarnykh VL, Johnson KM, Field AS, Alexander AL, Samsonov AA. Simultaneous variable flip angle-actual flip angle imaging method for improved accuracy and precision of three-dimensional T1 and B1 measurements. *Magn Reson Med* 2012;68(1):54-64.
4. Samsonov AA, Alexander AL, Velikina JV, Duncan ID, Field AS. Cross-relaxation imaging of age-related changes in myelin mutant shaking pup. Proceedings of the International Society for Magnetic Resonance in Medicine (ISMRM) 18<sup>th</sup> Scientific Meeting, Stockholm, Sweden, May 1-7, 2010:4515.
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7. Mossahebi P, Samsonov AA. Optimization Strategies for Accurate Quantitative MT Imaging. In: Proceedings of the International Society for Magnetic Resonance in Medicine (ISMRM) 20<sup>th</sup> Scientific Meeting, Melbourne, Australia, May 2012.
8. Mossahebi P, Alexander AL, Field AS, Samsonov AA. Quantitative Magnetization Transfer Imaging With Non-Exchanging Compartment Modeling: From CSF Partial Volume Correction to More Accurate Characterization of White Matter. In: Proceedings of the International Society for Magnetic Resonance in Medicine (ISMRM) 21<sup>st</sup> Scientific Meeting, Salt Lake City, Utah, April 2013.
9. Mossahebi P, Alexander AL, Field AS, Samsonov AA. Analysis and Optimization of Quantitative Magnetization Transfer Imaging Considering The Effect of Non-Exchanging Component. Accepted for presentation at the International Society for Magnetic Resonance in Medicine (ISMRM) 22<sup>nd</sup> Scientific Meeting, Milan, Italy, May 2014.
10. Wu YC, Alexander AL. Hybrid diffusion imaging. *Neuroimage* 2007;36:617-629.

11. Wu YC, Alexander AL, Duncan ID, Field AS. Hybrid diffusion imaging (HYDI) in a brain model of dysmyelination. In: Proceedings of the International Society for Magnetic Resonance in Medicine (ISMRM) 17th Scientific Meeting; 2009 April 18-24; Honolulu, Hawaii; 2009. p. 4176.
12. Wu Y-C, Field AS, Whalen PJ, Alexander AL. Age- and gender-related changes in the normal human brain using hybrid diffusion imaging (HYDI). *NeuroImage* 2011;54(3):1840-1853.